PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT EXAMINING OPERATION

First Named Inventor: Eric WICKSTROM

Serial No: 10/688,821 — Group Art Unit: 1633

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Att. Docket No.: W1133/20008 — Confirmation No.: 2530

For: COMPOUNDS AND METHODS FOR DIAGNOSTIC IMAGING AND THERAPY

PRE-APPEAL BRIEF REQUEST FOR REVIEW

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Commissioner for Patents
P.O. Box 1450
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Sir:

INTRODUCTORY COMMENTS

Applicant(s) hereby request(s) review of the Final Rejection in the above-identified application.

No amendments are being filed with this request.

This request is being filed with a Notice of Appeal.

The review is requested for the reason(s) stated on the attached sheet(s) entitled Remarks/Arguments in Support of the Pre-Appeal Brief Request for Review. The Remarks/Arguments section does not exceed five pages in length.

Respectfully submitted,

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May 19, 2008

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Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.

REMARKS/ARGUMENTS IN SUPPORT OF THE PRE-APPEAL BRIEF REQUEST FOR REVIEW

In response to the Final Office Action dated March 18, 2008, favorable reconsideration is respectfully requested in view of the following remarks. A Notice of Appeal in compliance with 37 C.F.R. 41.31 is filed concurrently herewith.

ERRORS IN THE EXAMINER'S REJECTIONS UNDER 35 U.S.C. § 103

Claims 1, 3, 4, 7-14, 16, 26-31, 34, 41-45, 48, 50, 52, 54-56, 69-73, 75, 80, 83, 86, and 88-101 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Tomalia et al. (U.S. Patent No. 5,714,166), in view of both Meade et al. (U.S. Patent No. 6,713,046) and Basu et al. Claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48, 49-52, 54-56, 69-73, 75, 80, 82, 83, 86, 88-101 were rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al., taken with both Meade et al. and Basu et al., in further view of Nakano et al. Claims 1, 3,4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 75, 80, 83, 86, 89-95 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Lewis et al., in view of both Liang et al. and Basu et al. Claims 1, 3, 4, 28-34, 41, 42, 48-52, 69, 71-73, 75, 80, 82, 83, 86, and 89-95 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Lewis et al. taken with Liang et al. and Basu et al., in further view of Nakano et al. Claims 1, 3, 4, 7-14, 16, 26-32, 34, 41-45, 48-52, 54-56, 69-73, 80, 83, 86, 88-101 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Lewis et al. taken with Liang et al. and Basu et al., in further view of both Tomalia et al. and Meade et al. It is respectfully requested that the Pre-Appeal Brief Review Conference Panel withdraw these rejections.

1. The Examiner argues that Tomalia et al. teaches a compound with the formula X-L1-T, wherein T can be a single-stranded nucleic acid, and that Tomalia et al. teach that the targeting moiety can be used to deliver the therapeutic moiety to a gene within the cell, i.e., antisense DNA, and concludes that Tomalia et al. teaches covalently binding nucleic acids to their dendrimers, wherein the nucleic acids can be used to deliver the therapeutic/diagnostic moiety to a specific target inside the cell. The Examiner admits that it does not specifically teach PNA, however, the Examiner argues that Basu et al. teach the advantages of using PNAs as compared to antisense DNA, and also teaches conjugating the PNA with a peptide analog of insulin-like growth factor 1 for increased cellular uptake of the PNA, wherein the PNA and the peptide analog are covalently linked by a (Gly)4 linker (Final Office Action at pages 6-7). The Examiner argues that Tomalia et al. teaches covalently binding nucleic acids to their dendrimers, wherein the nucleic acids can be used to deliver the therapeutic/diagnostic moiety to a specific target inside the

cell, and concludes that one of skill in the art would have known to replace the antisense DNA of Tomalia et al. with a PNA-peptide of Basu et al. The Examiner argues that by doing such, one of skill in the art would have obtained a compound having the formula X-L1-P-L2-T (Final Office Action at page 7).

2. However, Tomalia et al. specifically restricted "genetic materials" (which include PNA) as belonging to a class for which "formation of the complex does not take place via covalent bonding" ('166 Tomalia at column 47, lines 55-62). The other recitations of the (T)e*(P)x*(M)y structure ('166 Tomalia at column 2, lines 53-65, column 16, lines 31-52, column 22, lines 15-35, column 47, lines 1-10, column 52, lines 57-60) do not teach that M represents a PNA. At no point in the 5,714,166 patent does Tomalia et al. state that PNA, or any genetic material, can be covalently bonded to a dendrimer, not in the claims, not in the background, not in the examples.

3. The Examiner argues that the claims do not require a covalent bond to form X (i.e., attaching the therapeutic material to the dendrimer via a covalent bond) (Final Office Action at page 8). However, claim 1 specifically requires that L1 is covalently bound to X. Therefore, Tomalia et al. teaches away from covalent bonding of genetic materials to dendrimers.

4. Covalent bonding of L1 to X is tested in the present application by mass spectroscopy (see Specification at ¶[0066] and ¶[0181]; see also Tian, et al. (2004) Journal of Nuclear Medicine 45(12):2070-2082; Chakrabarti, et al. (2007) Cancer Biology & Therapy 6(6):948-956; Tian, et al. (2007) Journal of Nuclear Medicine 48(10):1699-1707, all cited in the IDS submitted 05-14-2007). Mass spectroscopic analyses consistently revealed covalent bonding, because the masses of the complete, purified probes agreed with the calculated masses.

5. Furthermore, Tomalia et al. actually teaches a compound with the formula (T)e*(P)x*(M)y (column 16, lines 37-52), (column 18, lines 23-67), (column 19, lines 1-67), (column 20, lines 1-29), (column 22, lines 20-26), wherein M represents a diagnostic or therapeutic agent, such as a radionuclide, T represents a target director, such as a moiety that can bind a cell-surface molecule, or a PNA that can bind a nucleic acid, P represents a dendrimer, and wherein M and T are associated with P via identical or different bonds, *. In contrast, the instant claims are directed to a compound X-L1-P-L2-T, wherein X represents a diagnostic or therapeutic agent, such as a radionuclide chelated to a dendrimer (comparable to P*M in Tomalia et al.), P represents a PNA that can bind a nucleic acid (comparable to T in Tomalia et al.), and T represents a cell surface target director, such as a moiety that can bind a cell-surface molecule (comparable to T in Tomalia et al.), and wherein X, P and T are associated with identical or different spacers L1 and L2 to prevent steric hindrance. The L1 and L2 spacers are a non-obvious solution, not

taught or suggested by Tomalia et al., or the combination of the references, to the problem of steric hindrance between the three functional units of the claimed compound.

6. Basu et al. reported a construct of the form P-L2-T designed to bind to a specific cellular receptor, internalize to the cytoplasm, and bind to its specific target mRNA. That construct does not contain a therapeutic or diagnostic moiety X and does not contain a spacer L1. One skilled in the art would therefore not have been motivated by Basu, et al. to covalently bond X-L1 to P-L2-T. As noted above, Tomalia et al. teach away from covalent bonding of genetic materials to dendrimers.

7. The Examiner argues that Lewis et al. and Liang et al. teach a targeting ligand capable of binding to a cell surface molecule. The Examiner states that the argument that the ligand of Liang et al. lacks the specificity provided by the present invention is not found persuasive because specificity is not claimed, and alleges that the claims only specify a targeting moiety capable of binding a cell surface molecule, which the transferrin of Liang et al. does. The Examiner also argues that even if the claims would recite specific delivery, it is noted that Basu et al. teach specific targeting moieties, and therefore, one of skill in the art would have known to use their targeting moiety to achieve delivery to specific cells (Final Office Action at page 11).

8. However, while the Examiner acknowledged that Lewis et al. "do not teach a targeting moiety capable of binding to a cell surface molecule (claim 1)" (Final Office Action at pages 7 and 8), the Examiner cites the Liang et al. reference to allegedly remedy the deficiency of Lewis et al. to teach the targeting moiety. Liang et al. teach construction of a transferrin-PNA conjugate associated with a plasmid DNA vector for the purpose of plasmid DNA vector delivery into cells to effect gene therapy. It is important to note that Liang et al. reported no cellular uptake of the transferrin-PNA:DNA conjugate until the cationic polymer polyethyleneimine (a detergent that facilitates DNA uptake into any cell) associated with a plasmid DNA vector was added (see Liang at page 240, Figure 5 and Figure 6). Liang et al. reported enhanced vector-encoded enzymatic activity in transfected cells if transferrin-PNA was associated with the plasmid DNA vector:polyethyleneimine complex. Therefore Liang et al. provide no motivation toward the design of the present diagnostic compound without the concurrent use of polyethyleneimine, which is not a targeting moiety. Furthermore, the toxicity of polyethyleneimine teaches away from utilizing the Liang et al. construct.

9. The Examiner argues that one of skill in the art would know that the DOTA of Lewis et al. could substitute for polyethyleneimine, since both are known in the art to be efficient at delivery of nucleic acids to the cells (Final Office Action at page 11). Unfortunately, equating DOTA with polyethyleneimine is a serious error. DOTA is a small, negatively charged circular molecule designed to bind positively

charged metal ions. DOTA has no ability to facilitate DNA uptake into any cell. Polyethyleneimine is a large positively charged detergent polymer that is designed to bind negatively charged polymers, like DNA, for the purpose of creating a neutral particle capable of facile cell penetration.

10. Lewis et al. teach a DOTA-PNA conjugate designed to target *bcl-2* (i.e., an oncogene), wherein DOTA comprises a radiometal (i.e., a polymeric diagnostic moiety) and wherein the PNA, which is 18 bases long, and is further coupled to a detergent-like PTD-4 peptide that facilitates intracellular delivery of the radiolabeled PNA (i.e., a targeting moiety) into any cell. The detergent-like PTD-4 peptide and DOTA are conjugated to PNA via linkers (Abstract, p. 1177, Fig. 1). The Examiner improperly equates a peptide detergent intended for universal intracellular delivery of the radiolabeled PNA (i.e., a membrane permeating peptide PTD-4) with a specific cell surface receptor targeting moiety of the present invention, which is defined in the specification on page 21, lines 20-21 as "a moiety that comprises any chemical substance that is capable of binding to a cell surface molecule or being bound by a cell surface molecule (e.g., a receptor)." In the instant invention, targeting the conjugate of the invention to a cell surface receptor so that the internalization is achieved via a receptor provides the desired specificity. This specificity cannot be achieved when a general membrane permeating peptide is used instead of a particular cell surface receptor ligand. Therefore, the membrane permeating peptide PTD-4 in Lewis et al. does not constitute a "targeting moiety" as contemplated in this invention.

11. The Examiner argues that one of skill in the art would have known and would have been motivated to use linkers to attach the targeting and therapeutic moieties to PNA, and that one of skill in the art would have known that, by doing so, functional interference between the PNA and the moieties attached to it would be avoided (Final Office Action at page 12). However, the Examiner erroneously equates a short bifunctional linker, *, intended only to connect the components of (T)e*(P)x*(M)y, with a flexible, hydrophilic spacer, L, 10-30 Å long, in X-L1-P-L2-T, intended to prevent functional interference between the PNA, P, and the moieties, X and T, attached to either end. Such spacers have only been introduced into such PNA constructs by the Applicants. Accordingly, the combination of the references does not teach or suggest all the claim limitations as asserted by the Examiner.

DECLARATION

12. If the Pre-Appeal Brief Review Conference Panel affirms any of the rejections of the present claims, Applicant relies upon **unexpected results** as shown in the Declaration under 37 CFR § 1.132 of Dr. Eric Wickstrom. The Federal Circuit has held that if a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. In re Gordon, 733 F.2d 900 (Fed. Cir. 1984), MPEP

2143.01. Here, the Examiner attempts to argue that Tomalia can be modified with the Meade and Basu patents to teach or suggest the claimed invention.

13. However, this modification would be unsatisfactory for its intended purpose, as demonstrated by the unsuccessful attempt by Applicant to synthesize a functional compound as claimed using the teachings or suggestions of Tomalia. In fact, Applicant had to completely alter the approach to synthesize the instantly claimed compound (Declaration at paragraphs 13-17). Here, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. See In re Ratti, 270 F.2d 810 (CCPA 1959). This is shown here.

14. With regard to the Declaration, the Examiner also argues that the Specification teaches that dendrimers can be prepared such that they have reactive groups capable of being attached to a variety of compounds including PNA and linkers and that techniques of attaching PNA to the dendrimers are within the skill in the art and concludes that the Declaration is not consistent with the teachings in the specification. (Final Office Action at page 8). However, as shown in the Declaration, Applicants' attempt to use the teachings of Tomalia to reach the claimed invention was unsuccessful, thereby showing that it would require a substantial reconstruction and redesign of the elements shown in the primary reference as well as a change in the basic principle under which the primary reference construction was designed to operate, as in the In re Ratti case, therefore the claims are patentable.

15. In addition, while obviousness does not require absolute predictability, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness, see In re Rinehart, 531 F.2d 1048 (CCPA 1976), MPEP 2143.02. Here, Applicants attempted to use the Tomalia teachings as the basis for to reach the claimed invention was unsuccessful, thereby showing that there was no reasonable expectation of success in modifying the Tomalia teachings. Therefore, the evidence provided by Applicant demonstrates that Applicant has attempted to utilize the PAMAM dendrimer according to the teachings of Tomalia, and that this attempt was unsuccessful.

Accordingly, the Pre-Appeal Brief Conference Panel is respectfully requested to withdraw the rejection(s) and pass this application to issuance.